

A genetic risk score predicts recurrent events after myocardial infarction in young patients with a low level of traditional risk factors

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Introduction: Coronary Heart Disease (CAD) is a multifactorial disease, including environmental and genetic risk factors. Current smoking, dyslipidemia and diabetes have a significant impact in long-term mortality and morbidity. However, several genetic variants associated with CAD but not with traditional risk factors (TRFs) has been reported to improve prediction of events and extended mortality, in younger CAD people.

Aim: To evaluate the clinical utility of a GRS composed by variants from GWAS associated to CAD but not with TRF to predict life-long residual risk in patients under 55 years old and a low level of TRFs.

Methods: We conducted a prospective study with 573 consecutive patients aged <55 years presenting with AMI and a low level of TRFs (without diabetes and with LDL cholesterol >150 mg/ml). We analysed several biochemical markers and performed a GRS with variants not associated with TRFs (TCF21 rs12190287, CDKN2B-AS1 rs1333049, CDKN2B rs4977574, PHACTR1 rs1332844, MIA3 rs17465637, ADAMTS7 rs3825807, ZC3HC1 rs11556924, SMAD3 rs17228212 and GJA4 rs618675). We studied the GRS association with a primary composite endpoint of all-cause vascular morbidity and mortality including recurrent acute coronary syndrome (myocardial infarct and unstable angina), coro-

nary revascularization (coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), re-hospitalization for heart failure, ischemic stroke and cardiovascular dead.

Results: A total of 573 patients were studied and followed up for a mean of 4.7±4.0 years. There were 169 recurrent cardiovascular events. The GRS was sub-divided into tertiles, verifying that patients in the third tertile (high risk) had a higher number of risk alleles. Compared with the low-risk GRS tertile, the multivariate-adjusted HR for recurrences was 1.520 (95% CI 1.011–2.286); p=0.044 for the intermediate-risk group and was 2.051 (95% CI 1.382–3.044); p<0.0001 for the high-risk group. Inclusion of the GRS in the model with TRFs alone (low risk) improved the C-statistic analysis (C-statistic = 0.030; p=0.004), cNRI (continuous net reclassification improvement) (30.8%), and the IDI (integrated discrimination improvement index) (0.022).

Conclusions: A multilocus GRS may identify young coronary disease patients with a low level of TRFs but at significant risk of long-term events recurrence. The genetic information may improve prediction discrimination, and reclassification over the conventional risk factors alone, providing better cost-effective therapeutic strategies.

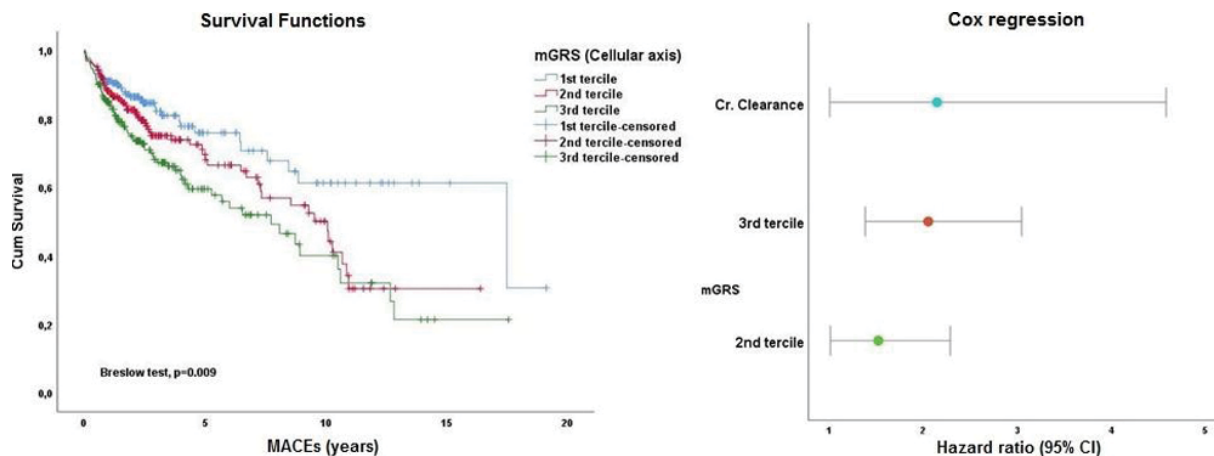


Figure 1